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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,322	11/12/2003	Thomas R. Gingeras	3535.1	2004

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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,322	GINGERAS, THOMAS R.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *3-6 and 20-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-19 and 24-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/12/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I (claims 2 and 19) in the reply filed on June 12, 2006 is acknowledged.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The specification does not claim priority to 60/442045. This can be remedied by amending the first paragraph of the specification to include such a reference.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1, 2, 7, 15, 16, 17, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Ren et al, (Science, (2000), volume 290, pages 2306-2309) as defined by Goffeau et al, (Science, (1996) volume 274, pages 546-567).

Claim 1 is drawn to a method of obtaining a plurality of functional regions of a genome and interrogating genetic variations of a plurality of individuals for these functional regions comprising at least 10,000 bases. The specification defines functional regions of the genome as, "associated with specific biological function." Functional regions given the broadest reasonable interpretation would encompass all genomic DNA, as genomic DNA functions in nucleosome and chromosome structure, transcriptional units, DNA replication and segregation, etc.

Claim 2 further limits claim 1 to a plurality of transcription factors.

With regards to claims 1 and 2, Ren teaches the identification of functional sites bound by the Gal4 transcriptional activator and Ste12 in the yeast genome (see abstract and figures 2 and 3). Ren teaches the use of triplicate samples of yeast grown in media with different carbon sources, broadly interpreted as a plurality of individuals (see figures 1 and 2). The yeast genome used by Ren, comprises 12,068 kilobases, as defined by Goffeau, which is a functional region of at least 5,000 bases (claim 17), 10,000 bases (claim 1), 100,000 bases (claim 15), 500,000 bases (claim 16) (see abstract).

Claims 7 and 24 require the use of microarrays to determine functional regions.

With regards to claims 7 and 24, Ren teaches the use of microarrays to determine DNA fragments to which proteins are crosslinked (see page 2306, column 2, lines 4-17). Ren teaches identification of promoter regions bound by transcription factors, STE12 and GAL4 (see abstract and figures 2 and 3).

4. Claims 1,2, 7, 15, 16, 17, and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Wyrick et al (US Patent 6410243) as defined by Goffeau et al, (Science, (1996) volume 274, pages 546-567).

Claim 1 is drawn to a method of obtaining a plurality of functional regions of a genome and interrogating genetic variations of a plurality of individuals for these functional regions comprising at least 10,00 bases.

Claim 2 further limits claim 1 to a plurality of transcription factors.

With regards to claims 1 and 2, Wyrick et al teaches the identification of functional regions of the genome to which proteins bind (see abstract and column 1 lines 36 and 37). Wyrick teaches the use of triplicate samples of yeast grown in media with different carbon sources, broadly interpreted as a plurality of individuals (see figure 2 and column 12 lines 17-19). The yeast genome used by Wyrick, comprises 12,068 kilobases, as defined by Goffeau, et al, which is a functional region of at least 5,000 bases (claim 17), 10,000 bases (claim 1), 100,000 bases (claim 15), 500,000 bases (claim 16) (see abstract).

Claims 7 and 24 require the use of microarrays to determine functional regions.

With regards to claims 7 and 24, Wyrick teaches, "a method of identifying region (one or more) of a genome of a cell to which a protein of interest binds" (see column 1 lines 36-38). Wyrick specifically teaches the identification of promoter regions bound by transcription factors, Gal4 and STE12 (see figures 6A and 7).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 8-12, 18, 19, and 25-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ren (Science, (2000), volume 290, pages 2306-2309) as defined by Goffeau et al, (Science, (1996) volume 274, pages 546-567) in view of Gentalen et al (US Patent 6306643).

Ren teaches the identification of functional sites bound by the Gal4 transcriptional activator and Ste12 in the yeast genome (see abstract and figures 2 and 3). Ren teaches the use of triplicate samples of yeast grown in media with different carbon sources, broadly interpreted as a plurality of individuals (see figures 1 and 2). The yeast genome used by Ren, comprises 12,068 kilobases, as defined by Goffeau, which is a functional region of at least 5,000 bases (claim 17), 10,000 bases (claim 1), 100,000 bases (claim 15), 500,000 bases (claim 16) (see abstract). Ren teaches the use of microarrays to determine DNA fragments to which proteins are crosslinked (see page 2306, column 2, lines 4-17). Ren teaches identification of promoter regions bound by transcription factors, STE and GAL4 (see abstract and figures 2 and 3).

Ren does not teach high-density arrays (claims 8 and 25), tiling arrays (claim 9 and 26) for the identification of the sequences (claim 10 and 27). Ren does not teach the use of tiling arrays for genotyping (claim 11 and 28) and SNP identification of

functional regions (claim 12 and 29). Ren also does not teach linkage analysis for transcription factor binding sites (claims 18, 19),

However, Gentalen teaches identifying various target sequences (column 1 lines22-23) by use of high density (claims 8, 9, 25, and 26)(see column 11, lines 18-20) tilling arrays (see figure 6 and column 15, lines 21-26) for simultaneous sequencing and mapping of numerous target sequences, (claims 10 and 27, see abstract, column 1 lines 65 and 66, and column 3 lines 62-62, column 15 lines 16-17). With regards to claims 11 and 28, Gentalen teaches a method of haplotyping using the array, haplotypes define genotypes (see column 8 lines 62 and 63). With regards to claims to claims 12 and 29, Gentalen teaches the identification of polymorphic sites (see column 8, lines 62 and 63). Gentalen teaches a SNP is a polymorphic site occupied by a single nucleotide (see column 7, lines 60 and 61). With regards to claims 18 and 19, Gentalen teaches linkage analysis from these methods for the identification of linkage disequilibrium of a SNP can be useful in detecting disease susceptibility, as it may identify a gene regulatory SNP which may be causative for the phenotype (see column 8, Lines 34-39). Gentalen teaches the use of high density tiling arrays to increase specificity of hybridization in mutation detection, better characterize repetitive sequences, and help contig assembly in sequencing by hybridization (see column 8 lines 61-65).

Therefore, it would be prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of functional region identification taught by Ren to incorporate Gentalen's high density tiling arrays in order to identify

sequence variations and analyze linkage markers (or SNPs), because Gentalen teaches detection of linkage disequilibrium between SNPs in regulatory sequences can be useful determining the causative element for a disease and disease susceptibility. The ordinary artisan would be motivated to improve Ren's method for functional region analysis, with the high density tiling arrays of Gentalen in order to identify causative elements of disease and disease susceptibility in regulatory sequences. It would further be prima facie obvious for the ordinary artisan at the time of the invention to improve Ren's method of functional regions analysis to incorporate Gentalen's method of haplotypes analysis, because Gentalen teaches it would allow determination of physical linkage of a marker, and further characterize the dependence of phenotype on genotype. One of ordinary skill in the art would be motivated to combine the functional regions analysis of Ren with the haplotyping methods of Gentalen in order to determine linkage, and further characterize the dependence of phenotype on genotype. It would further be prima facie obvious for one of ordinary skill in the art at the time of the invention to combine the high density tiling arrays taught by Gentalen with the functional region analysis of Ren, because Gentalen teaches the high density tiling arrays increase specificity of hybridization in SNP detection, better characterize repetitive sequences, and help contig assembly in sequencing by hybridization. The ordinary artisan at the time of the invention would be motivated to incorporate the high density tiling arrays of Gentalen, because Gentalen teaches high density tiling arrays increase specificity of hybridization in SNP detection, better characterize repetitive sequences, and help contig assembly in sequencing by hybridization (see column 8 lines 61-65). It

would be prima facie obvious for the ordinary artisan at the time the invention was made to incorporate the high density tiling arrays of Gentalen and the functional region analysis of Ren, because Gentalen teaches the artisan would be able to analyze substantially all sequences in human genome (see column 13 lines 64-66). The ordinary artisan would also be motivated to improve Ren's method of functional region analysis with the high density tiling arrays taught by Gentalen, because Gentalen teaches the artisan would be able to analyze substantially all sequences in human genome (see column 13 lines 64-66).

Claims 13, 14, 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ren as defined by Goffeau and Gentalen as applied to claims 8-12, 18, 19, and 25-29 above, and further in view of Rothberg et al (US Patent 5871697).

Claim 13 is drawn to the use of one restriction enzyme for the interrogation of functional regions by WGSA. WGSA is the use of a restriction enzyme to fragment DNA, followed by ligation of adapters and amplification to reduce complexity.

The teachings of Ren and Gentalen are set forth above. Ren and Gentalen do not teach the use of restrictions endonuclease, ligation of adapters and amplification (claims 13 and 30).

With regards to claims 13 and 30, Rothberg teaches the rapid, economical, quantitative and precise classification of DNA molecules by the use of restriction endonucleases to fragment a nucleic acid molecule to which recognition moieties are ligated, followed by amplification, preferably by polymerase chain reaction (see abstract and column 85, lines 60-63, column 86 lines 3 and 4, column 86 lines 35-50). Rothberg

teaches that this process, "generates precise, reproducible, noise free signatures... uniquely adaptable to automation" (see column 6 lines 10-14)

With regards to claims 14 and 31, Rothberg's method of classification allows for the identification of gene amplifications and/or loss of heterozygosity (see column 36, lines 62-68). Rothberg teaches gene amplifications and/or loss of heterozygosity of a disease state is useful in order to elucidate the genetic mechanism behind diseases (column 39 lines 9-12).

Therefore it would be prima facie obvious for one of ordinary skill in the art at the time the invention was made to improve the method of detecting transcription factor binding sites taught by Ren and Gentalen to incorporate the classification process taught by Rothberg because Rothberg teaches that the process, "generates precise, reproducible, noise free signatures... uniquely adaptable to automation" (see column 6 lines 10-14). The ordinary artisan would be motivated to improve the method of Ren and Gentalen with the classification process of Rothberg to allow for precise, reproducible, noise free signatures that are adaptable to automation. It would further be prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine functional region analysis of Ren and Gentalen with Rothberg's method of classification to examine gene amplification and/or loss of heterozygosity, because Rothberg teaches gene amplifications and/or loss of heterozygosity of a disease state is useful in order to elucidate the genetic mechanism behind diseases. The ordinary artisan would be motivated to combine Ren and Gentalen's functional region analysis

and Rothberg's method of classification because Rothberg teaches detection of gene amplifications/losses helps elucidate genetic mechanism behind diseases.

7. Claims 8-12, 18, 19, 25-29, are rejected under 35 U.S.C. 103(a) as being unpatentable over Wyrick as defined by Goffeau et al, (Science, (1996) volume 274, pages 546-567) in view of Gentalen et al (US Patent 6306643).

With regards to claims 1 and 2, Wyrick et al teaches the identification of functional regions of the genome to which proteins bind (see abstract and column 1 lines 36 and 37). Wyrick teaches the use of triplicate samples of yeast grown in media with different carbon sources, broadly interpreted as a plurality of individuals (see figure 2 and column 12 lines 17-19). The yeast genome used by Wyrick, comprises 12,068 kilobases, as defined by Goffeau, et al, which is a functional region of at least 5,000 bases (claim 17), 10,000 bases (claim 1), 100,000 bases (claim 15), 500,000 bases (claim 16) (see abstract). With regards to claims 7 and 24, Wyrick teaches, "a method of identifying region (one or more) of a genome of a cell to which a protein of interest binds" (see column 1 lines 36-38). Wyrick specifically teaches the identification of promoter regions bound by transcription factors, Gal4 and STE12 (see figures 6A and 7).

Wyrick does not teach high-density arrays (claims 8 and 25), tiling arrays (claim 9 and 26) for the identification of the sequences (claim 10 and 27). Wyrick does not teach the use of tiling arrays for genotyping (claim 11 and 28) and SNP identification of functional regions (claim 12 and 29). Wyrick also does not teach linkage analysis for transcription factor binding sites (claims 18, 19),

However, Gentalen teaches identifying various target sequences (column 1 lines22-23) by use of high density (claims 8, 9, 25, and 26)(see column 11, lines 18-20) tilling arrays (see figure 6 and column 15, lines 21-26) for simultaneous sequencing and mapping of numerous target sequences, (claims 10 and 27, see abstract, column 1 lines 65 and 66, and column 3 lines 62-62, column 15 lines 16-17). With regards to claims 11 and 28, Gentalen teaches a method of haplotyping using the array; haplotypes define genotypes (see column 8 lines 62 and 63). With regards to claims to claims 12 and 29, Gentalen teaches the identification of polymorphic sites (see column 8, lines 62 and 63). Gentalen teaches a SNP is a polymorphic site occupied by a single nucleotide (see column 7, lines 60 and 61). With regards to claims 18 and 19, Gentalen teaches linkage analysis from these methods for the identification of linkage disequilibrium of a SNP can be useful in detecting disease susceptibility, as it may identify a gene regulatory SNP which may be causative for the phenotype (see column 8, Lines 34-39). Gentalen teaches the use of high density tiling arrays to increase specificity of hybridization in mutation detection, better characterize repetitive sequences, and help contig assembly in sequencing by hybridization (see column 8 lines 61-65).

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be useful determining the causative element for a disease and disease susceptibility. The ordinary artisan would be motivated to improve Wyrick's method for functional region analysis, with the high density tiling arrays of Gentalen in order to identify causative elements of disease and disease susceptibility in regulatory sequences. It would further be prima facie obvious for the ordinary artisan at the time of the invention to improve Wyrick's method of functional regions analysis to incorporate Gentalen's method of haplotypes analysis, because Gentalen teaches it would allow determination of physical linkage of a marker, and further characterize the dependence of phenotype on genotype. One of ordinary skill in the art would be motivated to combine the functional regions analysis of Wyrick with the haplotyping methods of Gentalen in order to determine linkage, and further characterize the dependence of phenotype on genotype. It would further be prima facie obvious for one of ordinary skill in the art at the time of the invention to combine the high density tiling arrays taught by Gentalen with the functional region analysis of Wyrick because Gentalen teaches the high density tiling arrays increase specificity of hybridization in SNP detection, better characterize repetitive sequences, and help contig assembly in sequencing by hybridization. The ordinary artisan at the time of the invention would be motivated to incorporate the high density tiling arrays of Gentalen, because Gentalen teaches high density tiling arrays increase specificity of hybridization in SNP detection, better characterize repetitive sequences, and help contig assembly in sequencing by hybridization (see column 8 lines 61-65). It would be prima facie obvious for the ordinary artisan at the time the invention was made to incorporate the high density tiling arrays of Gentalen and the

functional region analysis of Wyrick, because Gentalen teaches the artisan would be able to analyze substantially all sequences in human genome (see column 13 lines 64-66). The ordinary artisan would also be motivated to improve Wyrick's method of functional region analysis with the high density tiling arrays taught by Gentalen, because Gentalen teaches the artisan would be able to analyze substantially all sequences in human genome (see column 13 lines 64-66).

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Conclusions

No claims are allowed due to prior art cited.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

JEHANNE SITTON
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8/04/06